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TITLE: Corrective <sup>111</sup>In Capromab Pendetide SPECT Image  
Reconstruction Methods for Improved Detection of Recurrent  
Prostate Cancer

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## INTRODUCTION

Prostate carcinoma, a leading cause for male cancer deaths, was estimated to result in 180,400 new cases and 31,900 deaths in the year 2000<sup>1</sup>. Earlier detection of prostate cancer has resulted from screening with serum prostate-specific antigen (PSA), with detection of disease when it is more localized<sup>2</sup>. In order to treat prostate cancer appropriately, it is essential to have accurate staging data. Clinicians try to determine tumor size and location, degree of periprostatic extension and whether bone and/or lymph node (LN) metastases are present. Imaging techniques routinely used for this purpose include transrectal ultrasound, pelvic CT and MRI, and radionuclide bone scanning. Despite these efforts, initial evaluation of pre-surgical patients leads to understaging in as high as 40 to 71% of patients<sup>3</sup>. Detection of LN metastases has been difficult, since LN involvement in prostate cancer is often associated with normal sized nodes. Since detection of LN disease with pelvic CT and MRI depends upon LN enlargement, neither of these modalities has been very successful in detecting the spread of prostate cancer to nodes (MRI slightly better than CT). Pooled data from four MRI series demonstrate an overall sensitivity of 42% and specificity of 98%<sup>4</sup>.

Imaging with <sup>111</sup>In capromab pendetide (PS), a monoclonal antibody agent utilizing an indium-labeled antibody to prostate-specific membrane antigen (present in increased amounts in prostate cancer cells) has proven useful in detecting LN metastases. It is particularly useful in the detection of recurrent prostate carcinoma in patients who have had radical prostatectomy for their disease, but who have increasing PSA levels indicating the presence of an additional tumor. In a multi-institutional study, <sup>111</sup>In PS scanning localized disease in 108 of 181 patients (60%) with uptake in the prostatic fossa in 62 patients (34%), pelvic LN in 40 patients (22%) and abdominal LN in 42 patients (23%)<sup>5</sup>. Results were evaluated for the prostate fossa by ultrasound guided biopsy: 59 patients had positive biopsies for recurrent tumor, but only 29 of these had positive scans for a sensitivity of 49%<sup>6</sup>. The investigators felt that the false negative scans were likely to be due to small tumor volume. Results are more difficult to confirm for disease outside the prostatic fossa, since the LN metastases will usually be too small for detection by CT or MRI.

It is generally recognized that <sup>111</sup>In PS scans are technically challenging to perform and interpret<sup>5</sup>, particularly with regard to the pelvic SPECT study used to detect possible disease in the prostate fossa and pelvic LN. Certainly part of this challenge is the detection of increased uptake in relatively small tumors in the pelvis.

In our preliminary study, we have demonstrated that corrective image reconstruction techniques that accurately correct for attenuation, collimator-detector response and scatter can significantly improve the quality and quantitative accuracy of <sup>111</sup>In PS SPECT images. The hypothesis of this proposal is that the superior spatial resolution, high image contrast, and much reduced image artifacts that result from the corrective SPECT image reconstruction methods would substantially aid in the detection and diagnosis of prostate cancer.

To test our hypothesis, we propose five specific aims: (1) to develop simulation tools and methods that allow efficient generation of accurate <sup>111</sup>In PS projection data from the human pelvic area, (2) to study the effects of 3D image degrading factors on <sup>111</sup>In PS SPECT images, (3) to develop 3D corrective image reconstruction methods for <sup>111</sup>In PS SPECT that provide much improved image quality and quantitative accuracy by incorporating models of the 3D image degrading factors, (4) to evaluate the 3D corrective image reconstruction methods for clinical <sup>111</sup>In PS SPECT studies using simulated populations of patient data, and Hotelling and human observer studies, and (5) to evaluate the clinical efficacy of the corrective image reconstruction methods as applied to <sup>111</sup>In PS SPECT using patient data.

## BODY

As we discussed in our first and second year report, our entire laboratory relocated from the University of North Carolina at Chapel Hill (UNC-CH) to Johns Hopkins University (JHU) in July 1,



2002. We had an extremely smooth transition and were able to continue the research project with minimal interruption. We submitted our second year progress report in March 2004. In the following, we describe the progress we have made during Year 3 of the project. The report addresses the specific tasks for Year 3 listed in the original proposal.

- Task 1. *To develop simulation tools and methods for  $^{111}\text{In}$  prostate SPECT (Months 1-18):*
- Extend the realistic NCAT phantom to include the pelvic region of the body (Months 1-12)*
  - Continue the development of a Monte Carlo simulation method that generates realistic projection data from the NCAT phantom with accurate models of the multiple photon emissions from  $^{111}\text{In}$ , their attenuation and scatter in the body, and the geometric, penetration and scatter response of the collimator (Months 4-18)*

Accomplishments:

1. We completed Task 1(a) in Year 1 as reported in the 1<sup>st</sup> year report.
2. We completed Task 1 (b) in Year 2 as reported in the 2<sup>nd</sup> year report.

- Task 2. *To study the effects of 3D image degrading factors on  $^{111}\text{In}$  prostate SPECT (Months 4-21):*
- Study the effect of photon attenuation in the patient's body on  $^{111}\text{In}$  SPECT images (Months 4-12)*
  - Study the effects of photon scatter in patient's body on  $^{111}\text{In}$  SPECT images (Months 7-15)*
  - Study the effects of collimator-detector response on  $^{111}\text{In}$  SPECT images (Months 10-18)*

Accomplishments:

1. We completed Task 2 (a), (b) and (c) in Year 1 and Year 2 as reported in the 1<sup>st</sup> and 2<sup>nd</sup> year report.

- Task 3. *To continue the development of 3D corrective image reconstruction methods for  $^{111}\text{In}$  prostate SPECT that provide much improved images quality and quantitative accuracy by incorporating models of the 3D image degrading factors (Months 7-24):*
- To use results from Task 2 to guide the development of methods to incorporate accurate models of image degrading factors in iterative and non-iterative 3D image reconstruction (Months 7-24)*

Accomplishments:

1. We completed Task 3 (a) in Year 1 and Year 2 as reported in the 1<sup>st</sup> and 2<sup>nd</sup> year report.

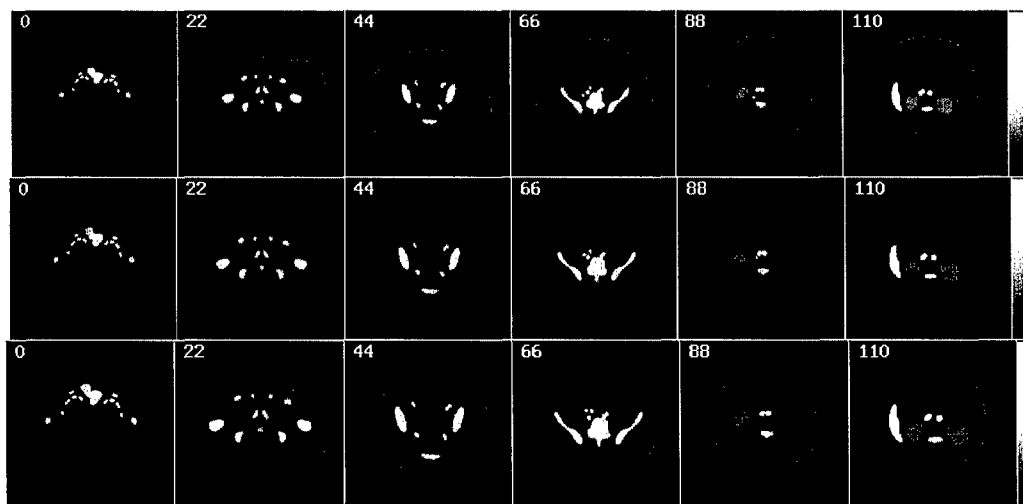
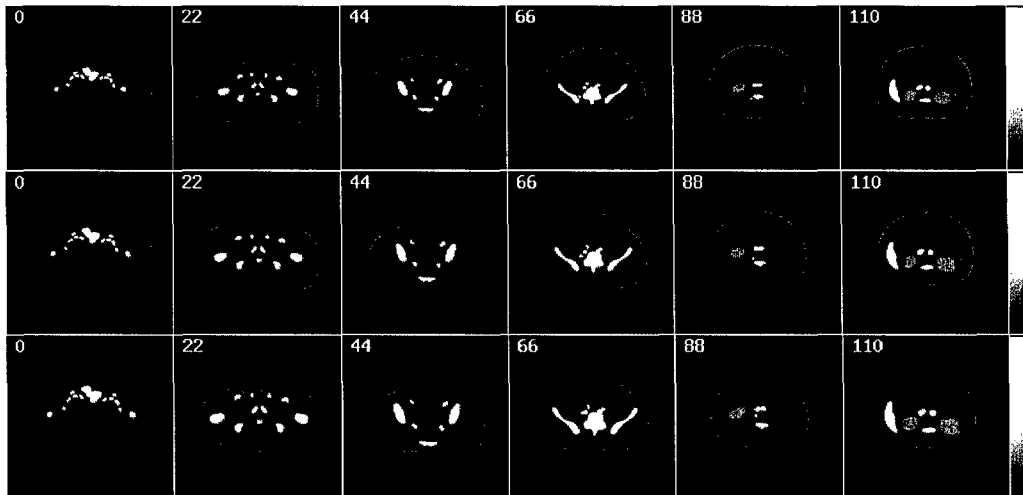
- Task 4. *To evaluate the 3D corrective image reconstruction methods for  $^{111}\text{In}$  prostate SPECT using simulated populations of patient data, and Hotelling and human observers (Month 13-36):*
- Evaluate the 3D corrective imaging reconstruction methods as applied to  $^{111}\text{In}$  prostate SPECT using Hotelling observers and ROC analysis methods (Months 13-36)*
  - Evaluate the 3D corrective imaging reconstruction methods as applied to  $^{111}\text{In}$  prostate SPECT using human observers and ROC analysis methods (Month 19-36)*

Accomplishments:

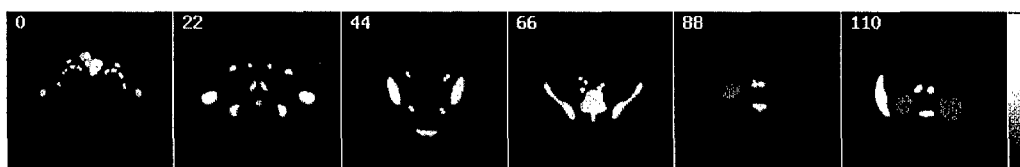
1. As indicated in the Year 2 report, we began simulating data required for the evaluation study and made significant progress. In Year 3, we have continued the effort and have been working on the full



scale data simulation for the Hotelling and human observer studies. Specifically, we have created a 'population' of phantoms that includes variations in patient anatomical structures as shown in Figure 1. The population consists of phantom with 3 body sizes, i.e., small, average and large, each with three different bone structure, i.e., small, medium and large. Also, to more realistically simulate patient data, we include possible air pockets in the intestines.







(c)

Figure 1. Family of 3D NCAT phantoms to be used in evaluation study with (a) small body size, (b) average body size, and (c) large body size. For each body size, (Top Row) small bone structure, (Middle Row) medium bone structure, and (Bottom Row) large bone structure.

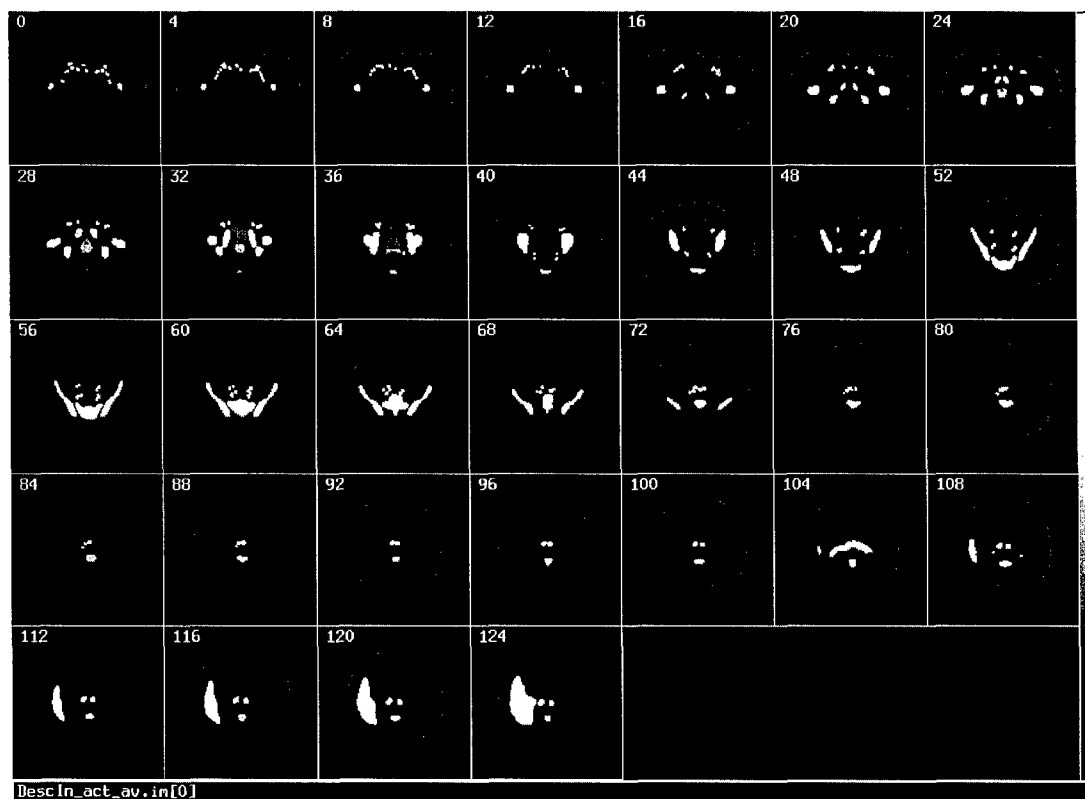


Figure 2. A 3D NCAT phantom that consists of air pockets in the intestines (the activity concentration is set to zero for easier visualization here; it is  $\sim 1:4$  with respect to background in actual simulation). It demonstrates our ability to simulation the special anatomy found in some patient studies.

2. We have carefully checked the quantitative SPECT image reconstruction methods developed in this research grant and applied them to the Monte Carlo simulated projection data from the 3D NCAT phantom described earlier. Figure 3 shows sample results from the Monte Carlo simulation study. The top two rows show sample slices through the 3D NCAT phantom showing the radioactivity and attenuation coefficient distribution of the phantom. The SimSET Monte Carlo code was used to generate 'almost' noise-free projection data from the 3D NCAT phantom. The noise-free projection data were scaled to specific mean counts and Poisson noise fluctuations were then added to simulate the acquired projection data. Finally, the quantitative SPECT image reconstruction methods were applied to obtain the reconstructed images at different iteration number. The simulation study allows comparison of the reconstructed images with the phantom slices and demonstrate the quality and quantitative accuracy of the quantitative SPECT image reconstruction methods.



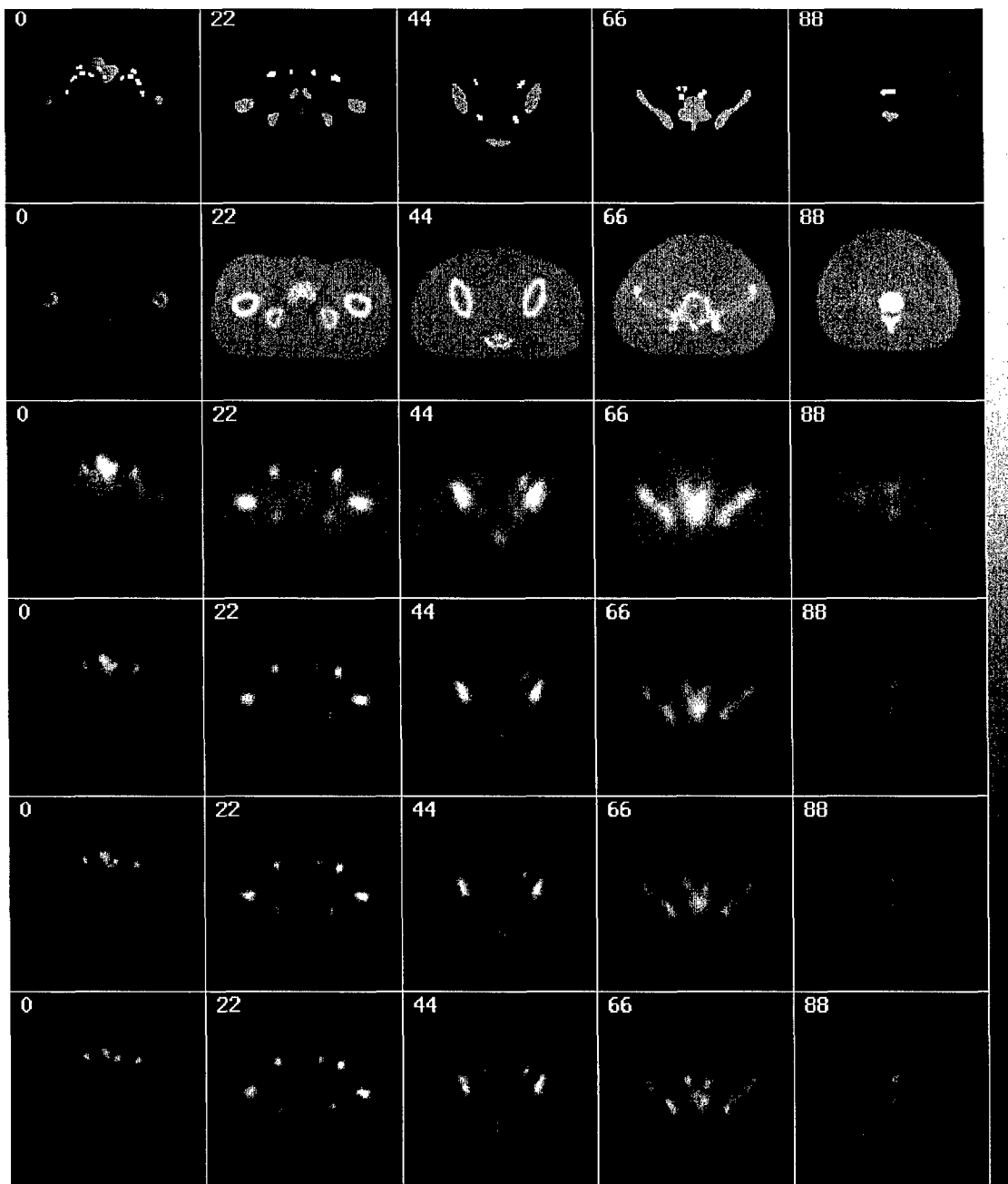


Figure 3. Sample reconstructed images obtained from applying the quantitative SPECT image reconstruction methods to the Monte Carlo simulated noisy projection data. *First Row:* Sample transaxial slices of the 3D NCAT phantom showing the radioactivity distribution. *Second Row:* Corresponding transaxial slices showing the attenuation coefficient distribution. Monte Carlo simulation method was used to generate 'almost' noise-free projection data that include the effects of attenuation, scatter and collimator-detector response of a medium-energy collimator. They were then scaled to a total projection count of 80K and Poisson noise fluctuations were added to simulate the actual acquired data. The quantitative SPECT image reconstruction methods, based on the iterative OS-EM algorithm with 6 subsets, 20 angular projections per subset and correction of attenuation and the collimator-detector response after *Third Row:* 1 iteration, *Fourth Row:* 2 iteration, *Fourth Row:* 2 iteration, *Fifth Row:* 4 iteration, and *Sixth Row:* 6 iterations.

3. We have made plan for the Hotelling observer study to evaluate the efficacy of the quantitative SPECT image reconstruction methods as applied to  $^{111}\text{In}$  labeled ProstaScint® SPECT images. The



null hypothesis is that there is no difference in lesion detectability (AUC) between the different reconstruction algorithms, i.e., filtered backprojection (FBP) with post-filtering using a Butterworth filter, the ordered-subsets expectation-maximization (OS-EM) algorithm with attenuation compensation (OSA), and OS-EM with attenuation and detector response compensation (OSAD).

To test this hypothesis, we propose to perform channelized Hotelling observer (CHO) study using simulated ProstaScint® data from a population of phantoms. The study consists of the following components.

- A. Create a population of phantoms as described in Accomplishment #1. The population of phantoms consists of anatomical variations.
- B. Vary the organ radionuclide uptake distribution (by randomly sampling from a distribution of uptake ratios) between phantoms, lesion size and location (3 different sizes & locations) and noise level, to mimic the variations seen in a human population.
- C. Simulate projection data from the phantom population so as to obtain two classes of images – lesion-present (LP) and lesion-absent (LA) – for use in the CHO study.
- D. Train the CHO with a training image set before applying it to test images.

The CHO study consists of the following sub-studies. These sub-studies are designed to determine the optimal image reconstruction parameters. The final result, that is, the best image reconstruction method will be derived from results of the sub-studies.

- To determine the optimal cut-off frequency for the Butterworth filter used in post-filtering of the FBP algorithm,
- To determine the optimal combination of iteration number and cut-off frequency for the Butterworth filter used in post-filtering of the OSA algorithm.
- To determine the optimal combination of iteration number and cut-off frequency for the Butterworth filter used in post-filtering of the OSAD algorithm.

The best image reconstruction method is the one that provides the highest lesion detectability, or largest area under the ROC curve, from the CHO studies.

The following list the details of the research plan. We are in the process of generating the projection data and reconstruction images for the study.

- A. Number of phantoms: (18 from the following, i.e., 3x3x2)
  - a. 3 body sizes: small, average, large
  - b. 3 body frames for each body size: small, medium, large
  - c. 2 intestinal states: air in ascending portion of large intestine, air pockets in descending portion, air in sigmoidal colon & rectum.
- B. Possible lymph node lesion locations: (3 as shown below and Figure 4)
  - a. Lesion in obturator node on the left side (slice 27)
  - b. Lesion in external iliac node on the right side (slice 45)
  - c. Lesion in common iliac node on the left side (slice 51)



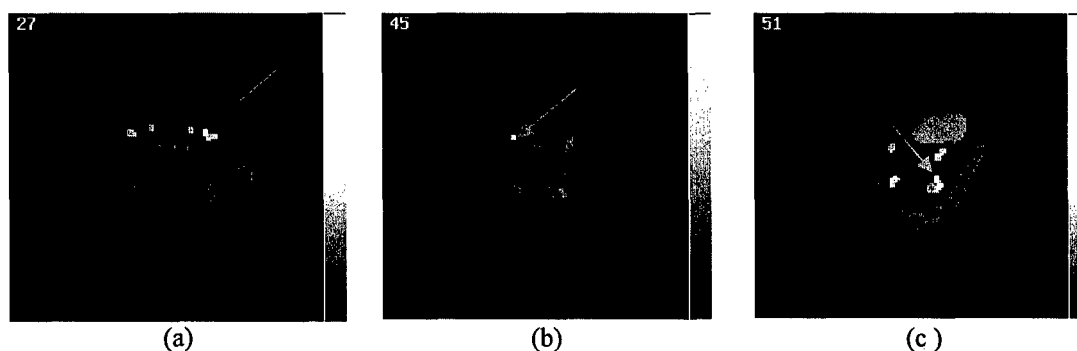
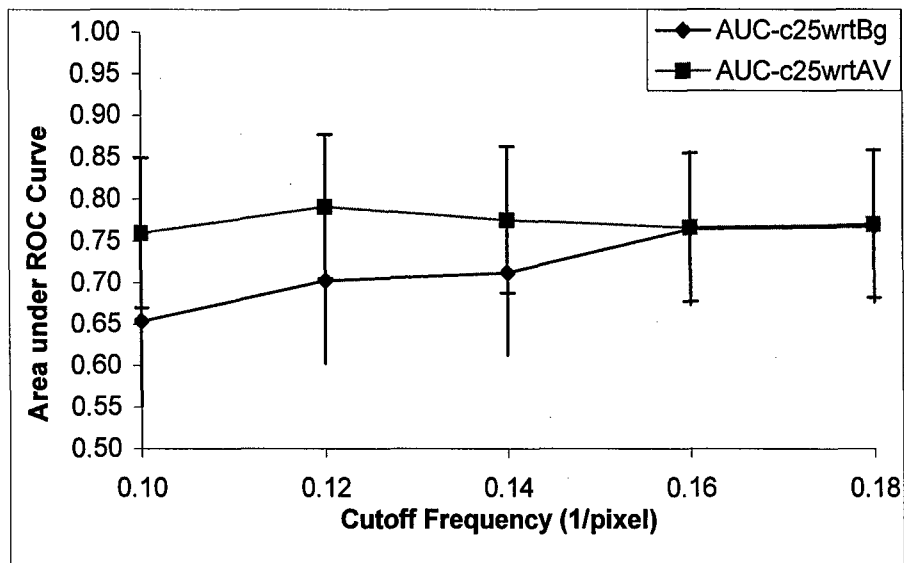


Figure 4. Possible lymph node lesion locations. (a) Lesion in obturator node on the left side (slice 27), (b) Lesion in external iliac node on the right side (slice 45), and Lesion in common iliac node on the left side (slice 51).

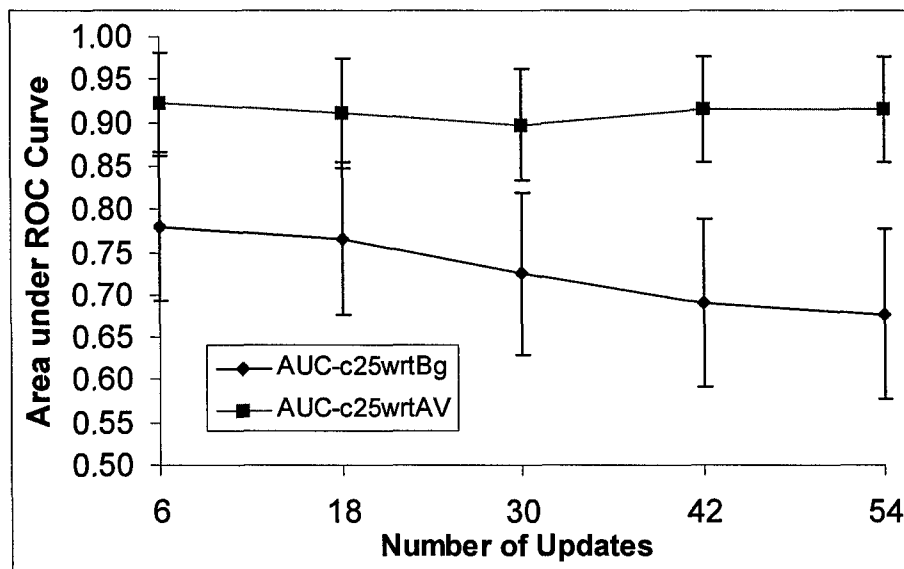
- C. Noise levels: (3 levels) at 7,000, 14,000 and 28,000 counts per slice
- D. Total number of images that will be generated: (Total of 324 LP and LA images)
  - Lesion present (LP): 18 phantoms x 3 lesions x 3 noise levels = 162 images; half of these (81) will be the LP images used for the training of the CHO, and the other half (81) will be used for testing.
  - Lesion absent (LA): 18 phantoms x 3 sets of noise realization (varied uptake ratios) x 3 noise levels = 162 images; half of these LA images will be used in training of the CHO, and the other half (81) will be used for testing.
- E. Total number of ROC curves that will be generated: (Total of 55 ROC curves)
  - Filtered Backprojection (FBP) with the Butterworth filter:  
5 filter cutoffs = 5 curves
  - OS-EM with attenuation correction (OSA) and Butterworth post-filtering:  
5 updates x 5 post-reconstruction filter cutoffs = 25 curves
  - OS-EM with attenuation and detector response correction (OSAD) and Butterworth postfiltering:  
5 updates x 5 post-reconstruction filter cutoffs = 25 curves
  - Total number of ROC curves that will be generated from this CHO study  
5 (FBP) + 25 (OS-A) + 25 (OS-AD) = 55
- F. Preliminary CHO study results

Figure 5 show preliminary result of the CHO studies. They are obtained with a small test image set resulting in a fairly large error bars. However, despite the relatively large error bars, the preliminary results indicate clearly the superior image quality in terms of detection of small lesions for the  $^{111}\text{In}$  PS SPECT images obtained with the quantitative SPECT image reconstruction methods as compared to the FBP algorithm without any correction. These preliminary results also demonstrate that all the components of the simulation study are working properly. Based on results of the preliminary study, we are proceeding onto the full scale simulation study using the CHO to evaluate the quantitative image reconstruction methods for prostate SPECT.



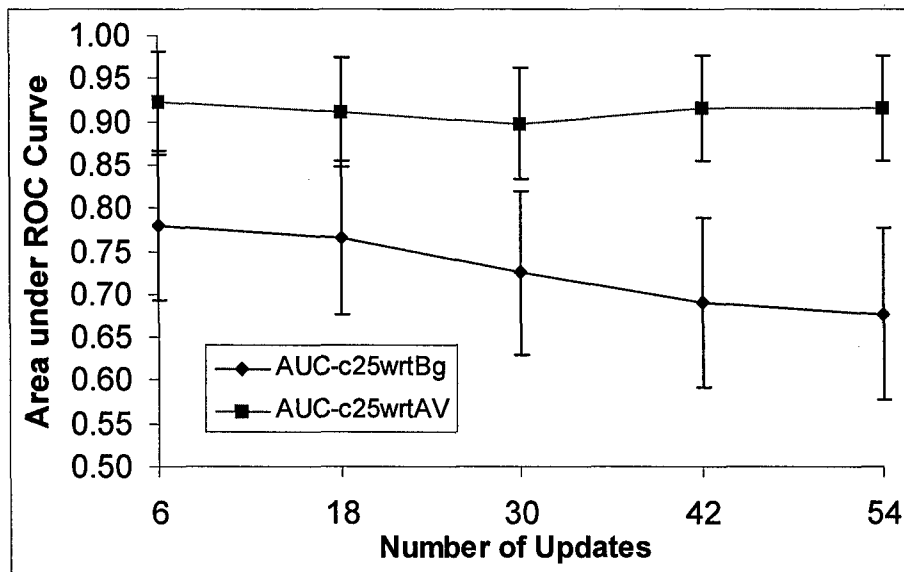


(a)



(b)





(c)

Figure 5. The areas under the ROC curve from the preliminary CHO study (a) as a function of cutoff frequency using the FBP algorithm without correction, (b) as a function of number of updates (number of subsets \* number of iterations) using the iterative OS-EM reconstruction algorithm, with compensation for attenuation (OSA), and (c) as a function of number of updates (number of subsets \* number of iterations) using the iterative OS-EM reconstruction algorithm, with compensation for attenuation and detector response (OSAD). The results in pink are from 25% lesion contrast with respect to background and the results in blue are with respect to the arteries & veins.

**Task 5.** To evaluate the clinical efficacy of the corrective image reconstruction methods using patient  $^{111}\text{In}$  prostate SPECT data (Month 1-36):

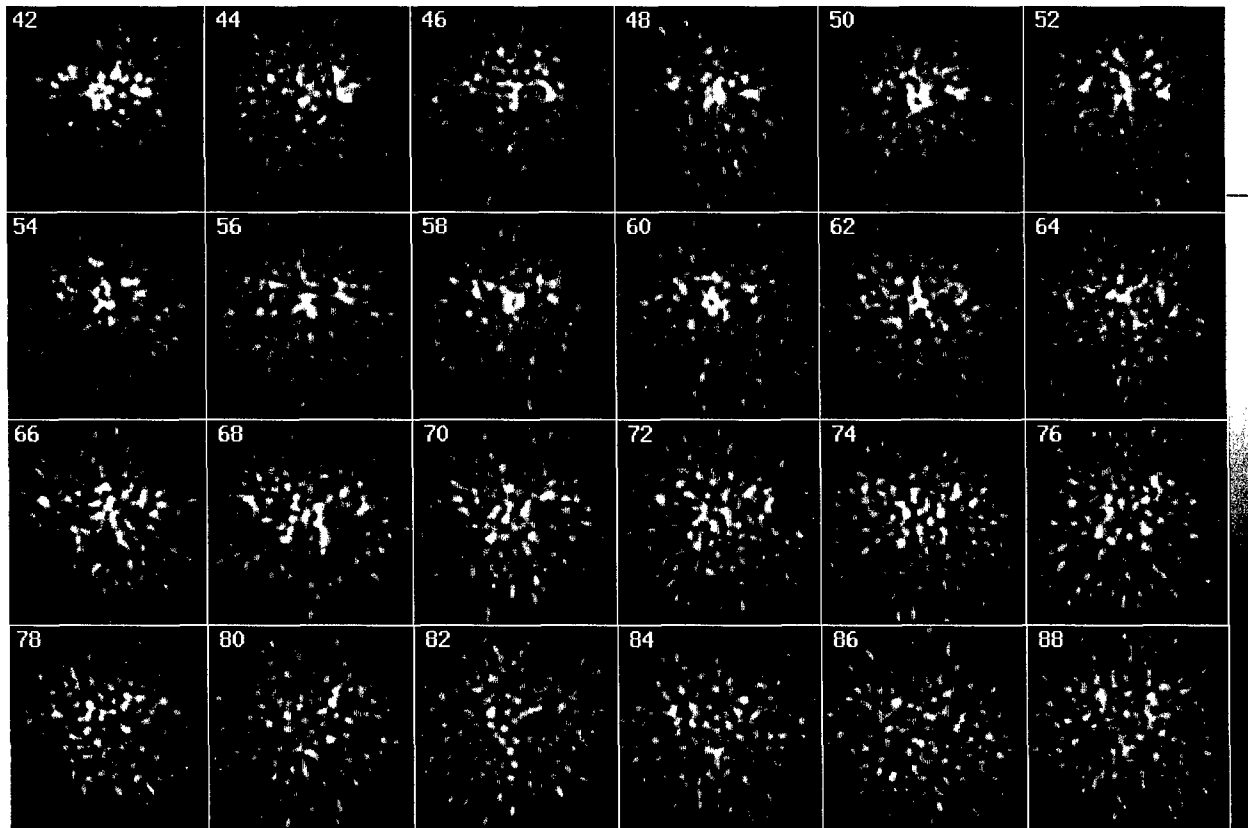
- To set up the GE VG/Hawkeye dual-head SPECT system for  $^{111}\text{In}$  PS SPECT data acquisition from patients (Month 1-3)
- To acquire  $^{111}\text{In}$  PS SPECT data acquisition from patients (Month 4-33)
- To process the patient  $^{111}\text{In}$  PS SPECT data using the corrective image reconstruction methods developed in Task 3 (Month 4-33)
- To conduct clinical evaluation of the patient  $^{111}\text{In}$  PS SPECT data (Month 13-33)
- Statistical analysis of evaluation data (Month 31-36)

#### Accomplishments:

- Task 5 (a) has been completed in Year 1.
- We have obtained IRB approval since our laboratory relocated to Johns Hopkins University (JHU). During Year 2, we have worked with the nuclear medicine clinic at JHU to modify the  $^{111}\text{In}$  PS SPECT data acquisition protocol to improve the quality of the acquired data. There is a slight delay in the clinical data acquisition due to the relocation and the application of the IRB. However, the official patient data acquisition and processing has begun.
- As of today, we have acquired data from 21 patient studies, i.e., 15 new cases during that last 12 months.
- We are in the process of checking the clinical data and applying the different image reconstruction methods.

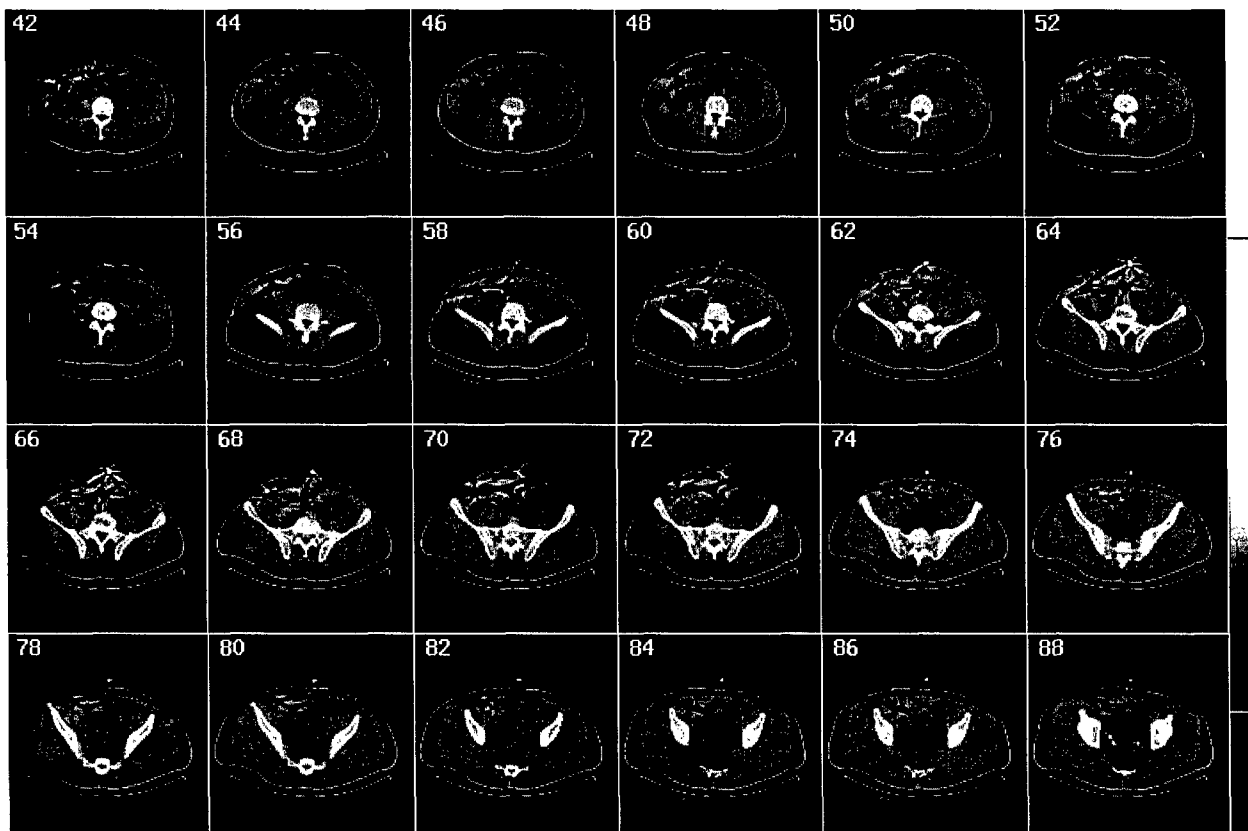


5. Also, we are planning on the clinical evaluation study using the clinical data and the patient record for the 'truth' state of the patients.
6. Figure 6 show a typical set of for  $^{111}\text{In}$  PS SPECT/CT images obtained from the patient study.

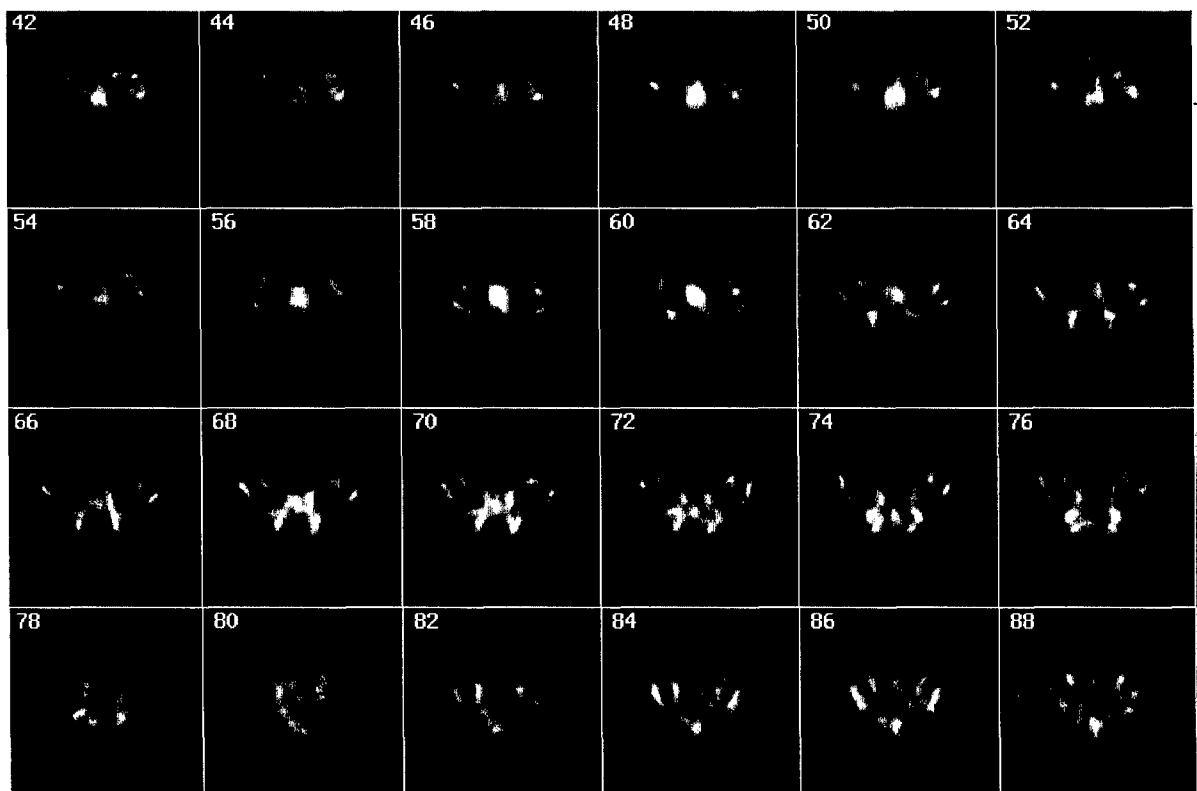


(a)





(b)



(c)





(d)

Figure 6. Results from one of the patient  $^{111}\text{In}$  PS SPECT studies obtained using a GE VG dual-head SPECT system equipped with a Hawkeye x-ray CT unit. The patient was injected with 5 mCi of  $^{111}\text{In}$  PS. The total data acquisition time was 35 minutes and a GE ME collimator was used. (a) Transaxial reconstructed images obtained using the conventional FBP reconstruction algorithm without any compensation. (b) Corresponding registered transmission CT images from the same patient. (c) Transaxial reconstructed images obtained using the iterative OS-EM algorithm with compensation of photon attenuation and scatter and the full collimator-detector response. Ten subsets and 5 iterations were used in the OS-EM reconstruction. Note the much improved image quality in terms of lower image noise and improved image resolution. (d) Fused SPECT/CT images.

## KEY RESEARCH ACCOMPLISHMENTS

1. Completed extension of the realistic 3D NCAT phantom to include the pelvic region of the body. The extended phantom includes the prostate gland, bladder, key blood vessels and major lymph nodes in the pelvic region.
2. Completed the development of a fast simulation method of realistic  $^{111}\text{In}$  PS projection data. The method is based on Monte Carlo simulation methods to simulation photon transport inside the phantom and the development of an angular response function (ARF) which accurately models the full imaging characteristics of the collimator-detector response function. The ARF is predetermined using Monte Carlo methods. The fast simulation method is 410 times faster than a straight Monte Carlo simulation method and provides the same accuracy and simulated image quality.
3. Completed the development of corrective image reconstruction methods that incorporate accurate compensation of photon attenuation and scatter in the patient and an accurate model of the full collimator-detector response. It is shown that the corrective image reconstruction methods provide substantial improvement in  $^{111}\text{In}$  PS prostate SPECT image quality.



4. Completed the design of the evaluation studies using Hotelling and human observers and to generate data for use in these studies.
5. Completed the creation of a population of 3D NCAT phantoms with variations of anatomy, organ radionuclide uptake distribution, lesion size and location and noise level, to mimic the variations seen in a human population.
6. In the process of generating simulated projection data from the phantom population so as to obtain two classes of images – lesion-present (LP) and lesion-absent (LA) – for use in the CHO study.
7. Work has begun to conduct the evaluation studies to determine the clinical efficacy of the quantitative SPECT image reconstruction methods for  $^{111}\text{In}$  PS SPECT imaging of the prostate.
8. Continuing acquisition of patient data and processing using the corrective image reconstruction methods have begun. Twenty-one patient studies have been collected and processed to-date.

## REPORTABLE OUTCOMES

### Manuscripts

1. Sayeram S, Tsui BMW, Zhao XD and Frey EC. Performance Evaluation of 3 Different SPECT Systems Used in In-111 ProstaScint SPECT Imaging. Conference Record of the 2003 IEEE Nuclear Science Symposium and Medical Imaging Conference, October 19-25, 2003, Portland, OR., page 1173, 2004.
2. Frey EC and Tsui BMW. Correction for Collimator Response Function in SPECT. (In) Quantitative Analysis of Nuclear Medicine Images. Kluwer Academic/Plenum Publishers, in press 2005.
3. Tsui BMW and Frey EC. Analytic Image Reconstruction Methods. (In) Quantitative Analysis of Nuclear Medicine Images. Kluwer Academic/Plenum Publishers, in press 2005.
4. Sayeram S, Tsui BMW, Zhao XD and Frey EC. Performance Evaluation of 3 Different SPECT Systems Used in In-111 ProstaScint SPECT Imaging. Manuscript submitted to IEEE Transactions in Nuclear Science, 2004.

### Presentations

1. Tsui BMW, Zhao X, Frey EC, Shao L, Aarsvold J, Durbin M, Alazraki N and Rollo FD, Evaluation of Quantitative Prostate SPECT/CT using In-111 ProstaScint®. Paper presented at the 51<sup>st</sup> Annual Meeting of the Society of Nuclear Medicine, Philadelphia, PA, June 19-23, 2004.
2. Sayeram S., Segars WP and Tsui BMW. Development and Evaluation of Simulated Phantoms for Use in In-111 ProstaScint® SPECT Imaging Studies. Paper to be presented at the 52<sup>nd</sup> Annual Meeting of the Society of Nuclear Medicine, Toronto, Canada, June 18-22, 2005.

## CONCLUSIONS

We have made significance progress in Year 3 of the project. The development of a fast simulation method of realistic  $^{111}\text{In}$  PS projection data was completed. The method is based on Monte Carlo simulation methods to simulation photon transport inside the phantom and the development of an angular response function (ARF) which accurately models the full imaging characteristics of the collimator-detector response function and is predetermined using Monte Carlo methods. The fast



simulation method is 410 times faster than a straight Monte Carlo simulation method and provide the same accuracy and simulated image quality.

We completed the development of corrective image reconstruction methods that incorporate accurate compensation of photon attenuation and scatter in the patient and an accurate model of the full collimator-detector response. It is shown the corrective image reconstruction methods provide substantial improvement in  $^{111}\text{In}$  PS prostate SPECT image quality.

We completed work on generating a population of 3D NCAT phantoms that realistically model the anatomical variations,  $^{111}\text{In}$  PS uptake distribution variations and lesion size and location in the patient population. We have started the channelized Hotelling observer experiments and preliminary results have been obtained that indicate the superior quality of the images obtained from the quantitative SPECT image reconstruction methods as compared to the conventional FBP algorithm without any corrections.

We are continuing the acquisition and processing of patient data using the corrective image reconstruction methods. Twenty-one patient studies have been collected to-date.

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